211. (Amended) A method for generating immune cells for autologous cellular immunotherapy, comprising:

collecting leukocyte containing material from a mammal;

differentiating the leukocytes into Th1 cells by contacting the cells with a composition comprising interferon-γ, or anti-Il-4 antibody or αB7.2 mAb or TGF-β; and

exposing the leukocyte containing material to two or more mitogenic different monoclonal antibodies to induce *in vitro* cell proliferation of Th1 cells sufficient for infusion into the mammal for use in an immunotherapy treatment, wherein the *in vitro* cell proliferation is produced without the use of exogenous interleukin-2.

REMARKS

A check for the fee for a three month extension of time accompanies this response. Any fee that may be due in connection with this application may be charged to Deposit Account No. Deposit Account No. 50-1213. If a Petition for extension of time is needed, this paper is to be considered such Petition.

Claims 22-25, 29, 31-33, 155-158, 165-168, 170-172, 211-213 and 216 are presently pending. Claims 22, 29, 155, 157, 170 and 211 are amended herein. Claims 28, 162-164, 216 and 217 are cancelled without prejudice or disclaimer.

Claims 22 and 155 are amended by incorporation of claims 28 and 163, respectively. Claim 211 is similarly amended. Claim 29 is amended to depend upon claim 22 rather than cancelled claim 28. Since claim 22 is amended to incorporate claim 29, amendment of claim 29 does not add new matter. Claim 170 is amended to eliminate non-elected subject matter. Basis for amendments of the claims also can be found in the specification at pages 28-34, which describes the agents and signals for Th1 cell differentiation and activation, page 38, which teaches that activation and expansion of the cells in the absence of Il-2 or other cytokines results in cells that upon reinfusion do not require co-

infusion of IL-2 for activity, page 15, which states "the infusion is not accompanied by co-infusion of a cytokine, such as IL-2", page 39 which states:

> [t]he methods herein do not rely or use any agents for expansion that must be present after expansion to maintain cell viability or activity. In particular, expansion does not require or use IL-2. As a result, re-infusion of the cells does not require or use IL-2, thereby obviating toxicity and other problems associated with IL-2 infusion.

Claims 162 and 164, which are allegedly drawn to non-elected subject matter, are cancelled. Amendment of claims 22 and 155 to incorporate cancelled claims 28 and 163, respectively, necessitates cancellation of claims 28 and 163 as duplicative. Claims 216 and 217, which are not properly dependent upon claim 22, are cancelled herein. The limitations of claim 217 is in claim 22. Applicant reserves the right to file divisional applications to the withdrawn subject matter; the Office is reminded that as between any of the cancelled claims and the presently pending claims obviousness-type double patenting cannot be held.

Claim 157 is indicated as being drawn to non-elected subject matter. Applicant does not understand the basis for this; hence claim 157, which is dependent on claim 155 is retained. If claim 155 is patentable, claim 157 must be patentable, since a dependent claim includes all limitations of the base claim.

Claims 212, 213, 215 and 216 are also retained. Claims 212 and 213 are dependent on claim 211; and claims 215 and 216 are dependent upon claim 22.

A marked up copy of claims showing the amendments herein is appended hereto.

Also provided herewith is an associate Power of Attorney appointing the undersigned to prosecute this application.

REJECTIONS UNDER 35 U.S.C. §112, FIRST PARAGRAPH

Claims 22-25, 28, 29, 31-33, 155-158, 162, 164-168, 170-172 are rejected under 35 U.S.C. §112, first paragraph, as containing subject matter that is allegedly not described in the specification in such as way as to reasonably convey that applicant had possess thereof at the time of filing on a

number of bases discussed in turn below. This rejection is respectfully traversed.

Relevant law

The purpose behind written description requirement is to ensure that the patent applicant had possession of the claimed subject mater at the time of filing of the application In re Wertheim, 541 F.2d 257, 262, 191 USPQ 90, 96 (CCPA 1976). The manner in which the specification meets the requirement is not material; it may be met by either an express or an implicit disclosure.

35 U.S.C. §112 requires a written description of the invention. This requirement is distinct from and not coterminous with the enablement requirement:

> The purpose of the 'written description' requirement is broader than to merely explain how to 'make and use'; the applicant must also convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." Vas-Cath, Inc. v. Mahurkar, 935 F.2d at 1563-64, 19 USPQ2d at 1117 (emphasis in original).

The issue with respect to 35 U.S.C. §112, first paragraph, adequate written description has been stated as:

> [d]oes the specification convey clearly to those skilled in the art, to whom it is addressed, in any way, the information that appellants invented that specific compound [claimed embodiment] Vas-Cath, Inc. v. Mahurkar, at 1115, quoting In re Ruschig, 390 F.2d 1990, at 995-996, 154 USPQ 118 at 123 (CCPA 1967).

A specification must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention, *i.e.*, whatever is now claimed. Vas-Cath, Inc. v. Mahurkar, 935 F.2d 1555, 1563-64, 19 USPQ.2d 1111, 1117 (Fed. Cir. 1991). A written description requirement issue generally involves the question of whether the subject matter of a claim is supported by or conforms to the disclosure of an application as filed. The test for sufficiency of support in a patent application is whether the disclosure of the application relied upon "reasonably conveys to the

artisan that the inventor had possession at that time of the later claimed subject matter." Ralston Purina Co. v. Far-Mar-Co., Inc., 772 F.2d 1570, 1575, 227 USPQ 177, 179 (Fed. Cir. 1985) (quoting In re Kaslow, 707 F.2d 1366, 1375, 217 USPQ 1089, 1096 (Fed. Cir. 1983)) (see also, MPEP 2163.02).

An objective standard for determining compliance with the written description requirement is "does the description clearly allow persons of skill in the art to recognize that he or she invented what is claimed." In re Gosteli, 872 F.2d 1008, 1012, 10 USPQ.2d 1614, 1618 (Fed. Cir.1989). The Examiner has the initial burden of presenting evidence or reasons why persons skilled in the art would not recognize in an applicant's disclosure a description of the invention defined by the claims. In re Wertheim, 541 F.2d 257, 265, 191 USPQ 90, 98 (CCPA 1976); *See also* Ex parte Sorenson, 3 USPQ.2d 1462, 1463 (Bd. Pat.App. & Inter. 1987). By disclosing in a patent application a device that inherently performs a function or has a property, operates according to a theory or has an advantage, a patent application necessarily discloses that function, theory or advantage, even though it says nothing explicit concerning it. The application may later be amended to recite the function, theory or advantage without introducing prohibited new matter. In re Reynolds, 443 F.2d 384, 170 USPQ 94 (CCPA 1971); and In re Smythe, 480 F. 2d 1376, 178 USPQ 279 (CCPA 1973).

Furthermore, the **subject matter of the claim need not be described literally (i.e., using the same terms or inhaec verba)** in order for the disclosure to satisfy the description requirement. If a claim is amended to include subject matter, limitations, or terminology not present in the application as filed, involving a departure from, addition to, or deletion from the disclosure of the application as filed, the examiner should conclude that the claimed subject matter is not described in that application. This conclusion will result in the rejection of the claims affected under 35 U.S.C.112, first paragraph - description requirement, or denial of the

benefit of the filing date of a previously filed application, as appropriate.

The guideline promulgated by the U.S. PTO embody these rules:

> In rejecting a claim, set forth express findings of fact regarding the above analysis which support the lack of written description conclusion. These findings should:
>
> (1) identify the claim limitation not described; and
>
> (2) provide reasons why a person skilled in the art at the time the application was filed would not have recognized the description of this limitation in view of the disclosure of the application as filed.

in this instance, there is not basis to conclude that a person skilled in the art at the time the application was filed would not have recognized the description of this limitation in view of the disclosure of the application as filed.

Analysis

1. The Examiner urges that the specification does not provide basis for the limitation in claim 22 that recites "in the absence of Il-2." Claim 22 is amended to recite "in the absence of exogenous Il-2", thereby obviating this rejection.

2. The Examiner urges that there is no basis in the application for the recitation of a method for production of Th1 cells at a density of 10^{10} cell/liter, wherein a homogeneous population of Th1 cells comprises greater than 50% Th1 cells." Applicant respectfully disagrees.

The specification provides basis for such limitation.

At page 39, the specification states:

> The compositions preferably contain substantially homogeneous populations of cells, such as Th1 cells or Th1-like cells, in which the cytokine profile is predominantly one type of cell (i.e., greater than about 50%). The compositions can contain regulatory immune cells, effector cells or both. In all instances the compositions contain clinically relevant, i.e., a therapeutically effective, numbers of cells.

Thus the compositions of cells provided in the application contain a substantially homogeneous population of cells, such as Th1 cells, in which there

is predominantly one type of cell. Predominantly one type of cell means greater than about 50%.

Further, at page 20, the specification states:

> As used herein, a composition containing a clinically relevant number or population of immune cells is a composition that contains at least 10^9, preferably greater than 10^9, more preferably at least 10^{10} cells, and most preferably more than 10^{10} cells, in which the majority of the cells have a defined regulatory or effector function, such as Th1 cells or Th2 cells or effector cells, such as LAK, TIL and CTL cells. . . . . The preferred number of cells will depend upon the ultimate use for which the composition is intended as will the type of cell. For example, if Th1 cells that are specific for a particular antigen are desired, then the population will contain greater than 50%, preferably greater than 70%, more preferably greater than 80%, most preferably greater than 90-95% of such cells. If the population results from polyclonal expansion, the homogeneous cells will be those that are a particular type or subtype. For uses provided herein, the cells are preferably in a volume of a liter or less, more preferably 500 mls or less, even more preferably 250 mls or less and most preferably about 100 mls or less.
>
> As used herein, predominant means greater than about 50%.

At page 21, line 26, - page 22, line 6, the specification states:

> . . . The therapeutically useful subpopulations are regulatory cells or effector cells and contain clinically relevant numbers of cells, typically at least about 10^9 or more cells, which are preferably in a clinically useful volume (i.e., for infusion) that is one liter or less.
>
> As used herein, a therapeutically effective number or clinically-relevant number ex vivo expanded cells is the number of such cells that is at least sufficient to achieve a desired therapeutic effect, when such cells are used in a particular method of ACT. Typically such number is at least 10^9, and more preferably 10^{10} or more. The precise number will depend upon the cell type and also the intended target or result.

See, also, page 34, lines 18-24, which describes the problems with low densities of cells, and see page 41, lines 1-12:

> T-cells, like most mammalian cells, will grow to a maximum density of 1×10^6 cells/ml in tissue culture. Thus, a total of 100 liters of culture medium would be required to support 100 billion cells. In addition, the

100 liters of medium would have to be replenished regularly to maintain a proper nutrient/waste product balance necessary to keep the cells viable. A method would also be required to keep the 100 liters of medium saturated with oxygen. . . .

1. Administration

The compositions of cell can be administered by any suitable means, including, but not limited to, intravenously, parenterally, or locally. The particular mode selected will depend upon the particular treatment and trafficking of the cells. Intravenous administration is presently preferred. Typically, about 10^{10}-10^{11} cells can be administered in a volume of a 50 ml to 1 liter, preferably about 50 ml to 250 ml., more preferably about 50 ml to 150 ml, and most preferably about 100 ml. The volume will depend upon the disorder treated and the route of administration. The cells may be administered in a single dose or in several doses over selected time intervals in order to titrate the dose, particularly when restoration of immune system balance is the goal.

At page 12, the specification states:

Also provided are methods for producing clinically relevant quantities (i.e., therapeutically effective numbers, typically greater than 10^9, preferably greater than 10^{10}) of autologous specific T cell types for treatment of disease states where a relative deficiency of such cells is observed. In particular, methods for producing clinically relevant numbers of autologous, ex vivo derived Th1 T-cells from patients with disease states where a Th2 cytokine profile predominates such as, but not limited to, infectious and allergic diseases; and autologous, ex vivo derived Th2 T-cells in Th1-dominant diseases, such as, but not limited to ,chronic inflammation and autoimmune diseases, for use in ACT protocols. The resulting cell compositions are provided and the use of the compositions in ACT protocols are provided.

Hence, the skilled artisan would recognize that methods for production of compositions that contain at least 10^{10} cells/liter of a homogeneous population of Th1 cells, where a homogeneous population is greater than about 50% in the composition.

3. The Examiner urges that in claims 155 and 157 there is no basis for recitation of in the absence of any exogenous cytokine. There is basis in the specification for such limitation. For example, at page 13, the specification states:

> Expansion is effected by growing the cells under conditions in which high cell densities can be achieved, whereby endogenous cytokines will be retained in the vicinity of the growing cell population, and in the presence of one or more mitogenic monoclonal antibodies or other cell surface specific protein, other than IL-2 or other such cytokine that will require co-infusion.

At page 15, the specification states:

> In particular, the infusion is not accompanied by co-infusion of a cytokine, such as IL-2.

Thus, the specification states that the expansion can be performed in the presence of one or more mitogenic antibodies or other cell surface protein, but not in the presence of IL-2 or other such cytokine.

Claims 22-25, 28, 29, 31-33, 155-158, 162, 164-168, 170-172, 211-213, 216 and 216 are rejected under 35 U.S.C. §112, first paragraph, as containing subject matter that is allegedly not described in the specification in such as way as to reasonably convey that applicant had possess thereof at the time of filing because the specification allegedly only discloses treatment with anti-Il-4 antibody, Il-12 or IFN-γ to induce differentiation of Th1 cells and the specific antibodies recited in claim 32 to induce expansion. This rejection is respectfully traversed.

The specification teaches a variety of was to induce differentiation. For example, at pages 29-30, the specification states:

> Accordingly, in a preferred embodiment, the mononuclear cells collected in the first step of the present process are next activated in the presence of IL-12, interferon-gamma or IL-4 to cause the development of Th1 or Th2 cells, respectively. To enhance the differentiation of regulatory cells, antibodies to IL-12 and/or interferon-gamma can be used to promote Th2 responses, while antibodies to IL-4 can be used to promote the differentiation of Th1 cells. Antibodies or other proteins specific for the IL-12, interferon-gamma or IL-4 receptor on T-cells could also be used to provide a signal in place of the lymphokines. The cells can be activated either non-specifically with chemical agents such as PHA and PMA or with monoclonal antibodies such as anti-CD3 or anti-CD2. Preferably, they are activated specifically with natural or man-made protein antigens added to the medium, processed and presented by APC

to T-cells. It may be necessary in some cases to vaccinate the patient prior to blood collection in order to increase the starting number of antigen-specific cells. Another strategy is to oral tolerize patients prior to blood collection. In cases where the cells generated are specific for a known antigen, the antigen may also be used after the cell reinfusion as a booster to increase the desired regulatory cells in vivo. Additional strategies for effecting Th1 cell differentiation is to activate cells in the presence of αB7.2 mAb or TGF-β. Th2 differentiation also can be promoted by activating cells in the presence of one or more of agents, such as, one or more of the following: αB7.1 mAb, low antigen doses and CTLA4/Ig fusion protein (CTLA4 is a ligand for CD28). CD28 is expressed on T-cells and antigen presenting cells.

The specification teaches a variety of ways to achieve differentiation and/or expansion. For example, at page 17, the specification teaches:

> As used herein, activating proteins are molecules that when contacted with a T-cell population cause the cells to proliferate. T-cells generally require two signals to proliferate. Activating proteins thus encompasses the combination of proteins that provide the requisite signals, which include an initial priming signal and a second co-stimulatory signal. The first signal requires a single agent, such as anti-CD3 mAb, anti-CD2 mAb, anti-TCR mAb, PHA, PMA, and other such signals. The second signal requires one or more agents, such as anti-CD28, anti-CD40L, cytokines and other such signals. Thus activating proteins include combinations of molecules including, but [are] not limited to: cell surface protein specific monoclonal antibodies, fusion proteins containing ligands for a cell surface protein, ligands for such cell surface proteins, or any molecule that specifically interacts with a cell surface receptor on a mononuclear cell and indirectly or directly causes that cell to proliferate.
>
> As used herein, a mitogenic monoclonal antibody is an activating protein that is an antibody that when contacted with a cell directly or indirectly provides one of the two requisite signals for T-cell mitogenesis. Generally such antibodies will specifically bind to a cell surface receptor thereby inducing signal transduction that leads to cell proliferation. Suitable mitogenic antibodies may be identified empirically by testing selected antibodies singly or in combination for the ability to increase numbers of a specific effector cell. Suitable mitogenic antibodies or combinations thereof will increase the number of cells in a selected time period, typically 1 to 10 days, by at least about 50%, preferably about 100% and more preferably 150-200% or more, compared to the numbers of cells in the absence of the antibody.

At pages 32-33, the specification teaches:

In order for T-cells to proliferate, they require two separate signals. The first signal is generally delivered through the CD3/TCR antigen complex on the surface of the cells. The second is generally provided through the IL-2 receptor. In order to bypass the IL-2 signal, combinations of mAb are used. Preferably, the mAb are in the soluble phase or immobilized on plastic or magnetic beads, in order to simplify the cell harvesting procedure.

(i) First signal

To provide the first signal, it is preferable to activate cells with mAb to the CD3/TCR complex, but other suitable signals, such as, but not limited to, antigens, super antigens, polyclonal activators, anti-CD2 and anti-TCR antibodies, may be used. Other suitable agents can be empirically identified. Immobilized or cross-linked anti-CD3 mAb, such as OKT3 or 64.1, can activate T-cells in a polyclonal manner [see, Tax, et al. (1983) Nature 304:445]. Other polyclonal activators, however, such as phorbol myristate acetate can also be used [see, e.g., Hansen, et al. (1980) Immunogenetics 10:247]. Monovalent anti-CD3 mAb in the soluble phase can also be used to activate T-cells [see, Tamura, et al. (1992) J. Immunol. 148:2370]. Stimulation of CD4+ cells with monovalent anti-CD3 mAb in the soluble form is preferable for expansion of Th2 cells, but not Th1 cells [see, deJong, et al. (1992) J. Immunol. 149:2795]. Soluble heteroconjugates of anti-CD3 and anti-T-cell surface antigen mAb can preferentially activate a particular T-cell subset [see, Ledbetter, et al. (1988) Eur. S. Immunol. 18:525]. Anti-CD2 mAb can also activate T-cells [see, Huet, et al. (1986) J. Immunol. 137:1420]. Anti-MHC class II mAb can have a synergistic effect with anti-CD3 in inducing T-cell proliferation [see, Spertini, et al. (1992) J. Immunol. 149:65]. Anti-CD44 mAb can activate T-cells in a fashion similar to anti-CD3 mAb. See, Galandrini, et al. (1993) J. Immunol. 150:4225].

For purposes herein, monoclonal antibodies to anti-CD3 are preferred. Anti-CD3 is used because CD3 is adjacent to the T-cell receptor. Triggering of CD3, such as by monoclonal antibody interaction, causes concomitant T cell activation.

(ii) Second signal

To then cause proliferation of such activated T cells, a second signal is required. A variety of mAb singly or in combination can provide the second signal for T-cell proliferation. Anti-IL-4R mAb (specific for the interleukin-4 receptor molecule) can enhance the proliferation of the Th2 cells [see, Lindquist, et al. (1993) J. Immunol. 150:394]. Immobilized ligands or mAb against CD4, CD8, CD11a (LFA-1), CD49 (VLA),

> CD45RO, CD44 and CD28 can also be used to enhance T-cell proliferation [see, Manger, et al. (1985) J. Immunol. 135:3669; Hara, et al. (1985) J. Exp. Med. 161:1513; Shimizu, et al. (1990) J. Immunol. 145:59; and Springer, (1990) Nature 346:425]. Cell surface proteins that are ligans to B-cells are preferred targets for Th2 cell proliferation, while macrophage ligands are preferred for Th1 cell proliferation.
>
> Anti-CD28 mAb in combination with anti-CD3 or anti-CD2 induces a long lasting T-cell proliferative response [see, Pierres, et al. (1988) Eur. J. Immunol. 18:685]. Anti-CD28 mAb in combination with anti-CD5 mAb results in an enhanced proliferative response that can be sustained for weeks [see, Ledbetter, et al. (1985) J. Immunol. 135:2331]. Anti-CD5 mAb alone can also provide a second signal for T-cell proliferation [see, Vandenberghe et al. (1991) Eur. J. Immunol. 21:251]. Other mAb known to support T-cell proliferation include anti-CD45 and CD27 [see, Ledbetter, et al. (1985) J. Immunol. 135:1819 and Van Lier, et al. (1987) J. Immunol. 139:1589].
>
> To determine the combination of mAbs or proteins that optimally induce sustained regulatory cell proliferation, a screening procedure using combinations of these mAbs or proteins is used. The cells are incubated with various combinations of these substances and screened for growth by analysis of ^{3}H-thymidine incorporation or equivalent methods. The group demonstrating the best growth characteristics is selected for use in the medium.

Thus, the specification describes a variety of different agents and combinations thereof for activating and causing proliferation of Th1 cells, and teaches ways for empirically identifying additional agents.

Furthermore, the claims (see original claim 1) as originally filed recite that the method is performed by:

> contacting, in the absence of exogenous interleukin-2, the material with one or more activating proteins specific for cell surface proteins present on cells in the material and in an amount sufficient to induce ex vivo cell expansion, whereby the cells expand to clinically relevant numbers.

Original claim 3 recites:

> The method of claim 1, wherein during the contacting step, the cells in the material are treated under conditions, other than addition of

exogenous IL-2, whereby ex vivo differentiation of some or all of the c lls into desired effector immune cells is induced.

Original claim 8 recites that the expandedcells are Th1 cells.

Hence, it is clear that applicant appreciated and had possession of the subject matter as claimed at the time of filing of this application and the parent application.

BASIS IN PARENT APPLICATION

It is respectfully submitted that pending claims do indeed find basis in the parent application. As discussed previously, the test for new matter is that the specification must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention, *i.e.*, whatever is now claimed. Vas-Cath, Inc. v. Mahurkar, 935 F.2d 1555, 1563-64, 19 USPQ.2d 1111, 1117 (Fed. Cir. 1991). The specification as originally filed conveys with reasonable clarity disclosure that supports all of the pending claims and the claims of this application as originally filed.

In the parent application, U.S. provisional application Serial No. 60/044,693 (converted to a provisional from application Serial No. 08/506,608) claim 1 recites:

1. A method for generating autologous effector immune cells, the method comprising:

collecting material leukocyte containing material from a mammal; and
exposing the leukocyte containing material to mitogenic monoclonal antibodies to induce *in vitro* cell proliferation sufficient for infusion into the mammal for use in an immunotherapy treatment, wherein the *in vitro* cell proliferation is produced without the use of exogenous interleukin-2.

Claim 2 of the parent application recites:

2. The method of claim 1, wherein the leukocyte containing material is caused to differentiate into desired effector cells.

Hence claim 2 corresponds to presently pending claim 211, which has been amended to recite Th1 cells (see, claim 7 in the parent application, which

includes Th1 and Th2 cells as species of effector cells, under the old definition).

Claim 14 recites that the cells are proliferated to "an excess of 1×10^{10} cells."

Claim 7 recites that the cells are Th1-like or Th2-like cells, thereby indicating that as originally filed, what are now called regulatory cells were contemplated to be within the scope of the original claims and to be separately claimed.

The parent application is directed to methods for the production of high concentrations and amounts of homogeneous compositions of immune cells, including Th1, Th2, and also LAK, CTL and TIL cells. In the parent application, the term "effector" cell was used to encompass all types. Dependent claims separated out the Th1 and Th2 cells from the generic type. Claim 1 generically encompassed all types of cells.

In the instant application, the nomenclature, **not** the intended scope of the claims, was modified so that the generic language refers to what was called effector cells in the parent application as "immune cells" Compare claim 1 as originally in the instant case with claim 1 of the parent case. The language "effector" is changed to immune cell. Further, two classes of cells were defined: regulatory immune cells, which are clearly defined (as discussed below) to include Th1 and Th2 cells, which can be identified by their distinct cytokine profiles and which act on other cells; and effector immune cells, which are defined as the LAK and TIL type cells.

The parent specification states at page 7, line 16. that effector cells include Th1, Th2-like cells. The specification describes Th1 and Th2 cells at page 8, lines 27, page 9, line 3, and page 9, lines 20-24; and states at page 9, lines 25-28:

> Accordingly, it is desirable to have the ability to produce large quantities of autologous Th1 T-cells in disease states where a Th2 cytokine profile predominates (infectious disease) and Th2 T-cells in a TH1-dominant disease (chronic inflammation and autoimmune disease).

Methods for differentiation of immune cells into Th1 or Th2 cells are described at page 11, lines 11-19.

The scope of the claims and subject matter of the claims as originally filed and as filed in the instant cased are the same. The definitions were slightly modified in the instant case; but it is clear from the context that the broad claims and dependent claims are the same.

The parent application states, starting at page 6, line 23, that:

> use of ACI protocols will require technology that enables: the generation of homogeneous populations of immune effector cells [*i.e.*, cells that include TILs, LAKs, CTLs, Th1, Th2 cells]; the consistent growth of effector cells to clinically relevant dosages (*i.e.*, greater than 10^{10} cells) without the use of IL-2; . . . and the ability to reinfuse the cells without the need for systemic infusion of IL-2. Furthermore additional *in vitro* differentiation strategies are need to broaden the types of cells available for ACI protocols.

The present invention addresses each of these requirements, disclosing a method to differentiate Th1 or TH2 cells *in vitro* and grow these cells to clinically relevant numbers without the use of IL-2.
This provides clear unequivocal basis for claim 1 in the present application.

The instant application has been rewritten for clarity, not to add new matter to the claims, and to provide additional supporting examples. To distinguish between differentiation of cells to produce LAKs, TILs and CTLs, from differentiation to produce Th1, Th2 and Th3 cells and subcategories thereof, different nomenclature has been adopted. The same cells are encompassed by the claims; their names are different. Changing the names of claimed subject matter does not add new matter if the substance remains substantially the same.

Similarly, claim 155 and 197 find basis in the parent application. Claim 155 recites:

155. (Amended) A method for generating clinically relevant numbers of Th1 cells for autologous cell therapy, comprising:

(a) collecting material comprising body fluid or tissue containing mononuclear cells from a mammal;

(b) treating the cells to induce differentiation of mononuclear cells into Th1 cells, wherein the cells are treated with either or both interferon-γ and IL-2 to induce differentiation of Th1 cells or the . and

(c) contacting the resulting differentiated cells with two or more activating proteins specific for cell surface proteins present on the cells in an amount sufficient to induce *ex vivo* cell expansion, whereby clinically relevant numbers of cells for autologous cell therapy are generated, wherein the contacting is effected in the absence of exogenous IL-2.

Basis for claim 155 may be found in original claim 2, which includes the steps of obtaining the cells (see, also page 10, lines 15-20, which describes the step of obtaining mononuclear cells), causing them to differentiate (see, also page 10, line 25, - page 11, line 21 which describes means to cause differentiation of the collected cells into various cell types, including using Il-2) and expanding the differentiated cells. Basis for claim 197 may be found in original claim 2.

As noted, in the interest of advancing prosecution (not to alter the scope or content of the claims), the word "regulatory" or "effector" no longer appears in the claims, thereby rendering the issue with respect to nomenclature moot. The word regulatory is not needed, since the claims now specifically recite Th1 cells in order to conform the case to the elected subject matter. Conforming claims to a requirement for election **cannot then result in an assertion by the Patent Office that such amendment adds new matter**; if it does, then the requirement for election is improper.

Furthermore, by reciting the names of the cells rather then their functional definition, it does not matter whether they are called effector cells (under older

art definitions) or regulatory cells under current definitions. They are the same cells and would be the same cells (*i.e.* Th1 cells), if the were called "Fred or Harry." Th1 cells are the among the cells that can are produced by the methods herein.

THE REJECTION OF CLAIMS 22-25, 28, 31, 32, 155-158, 164, 165, 167, 168, 211, 212 and 216 UNDER 35 U.S.C. § 102(e)

Claims 22-25, 28, 211 and 216

Claims 22-25, 28, 211 and 216 are rejected under 35 U.S.C. § 102(e) as being anticipated by Babbitt *et al.* (U.S. Patent No. 5,766,920) because Babbitt *et al.* allegedly discloses a method for production of Th1 cells in which mononuclear cells are removed and expanded *in vitro* for use in autologous cell therapy. The Examiner urges that the expansion is effected in the absence of IL-2 and that Babbitt *et al.* discloses the use of IFN-γ supernatants and OKT3 to produce Th1 cell populations. The particulars of the Examiner's rejection are addressed below.

This rejection is respectfully traversed.

Relevant law

Anticipation requires the disclosure in a single prior art reference of each element of the claim under consideration. In re Spada, 15 USPQ2d 1655 (Fed. Cir, 1990), In re Bond, 15 USPQ 1566 (Fed. Cir. 1990), Soundscriber Corp. v. U.S.. 360 F.2d 954, 148 USPQ 298, 301, adopted 149 USPQ 640 (Ct. Cl.) 1966. See, also, Richardson v. Suzuki Motor Co., 868 F.2d 1226, 1236, 9 USPQ2d 1913,1920 (Fed. Cir.), cert. denied, 110 S.Ct. 154 (1989). "[A]ll limitations in the claims must be found in the reference, since the claims measure the invention". In re Lang, 644 F.2d 856, 862, 209 USPQ 288, 293 (CCPA 1981). Moreover it is incumbent on Examiner to identify wherein each and every facet of the claimed invention is disclosed in the reference. Lindemann Maschinen-fabrik Gmbh v. American Hoist and Derrick Co., 730 F.2d 1452, 221 USPQ 481 (Fed. Cir. 1984). Further, the reference must describe

the invention as claimed sufficiently to have placed a person of ordinary skill in the art in possession of the invention. An inherent property has to flow naturally from what is taught in a reference In re Oelrich, 666 F.2d 578, 581, 212 USPQ 323, 326 (CCPA 1981).

Claims

Claim 22 is directed to a method for generating clinically relevant cell numbers of Th1 cells. The steps of the method include:

(a) collecting material containing mononuclear T lymphoid cells from a mammal;

(b) activating the T lymphoid cells to alter their cytokine production profile by causing differentiation of the cells into Th1 cell, wherein the cell are activated in the presence of either or both interferon-γ and IL-2 or anti-Il-4 antibody or αB7.2 mAb or TGF-β, whereby cells differentiate into Th1 cells; and

(c) in the absence of exogenous Il-2, inducing cell proliferation and expanding the cells under conditions that produce at least about 10^{10} cells/liter of a homogeneous population of Th1 cells, wherein a homogeneous population of Th1 cells comprises greater than about 50% Th1 cells.

Dependent claims specify particulars, including the volume of the resulting population of cells.

Claim 211 is directed to a method for generating immune cells for autologous cellular immunotherapy, by:

> collecting leukocyte containing material from a mammal;
>
> differentiating the leukocytes into Th1 cells by contacting the cells with a composition comprising interferon-γ, or anti-Il-4 antibody or αB7.2 mAb or TGF-β; and
>
> exposing the leukocyte containing material to two or more mitogenic monoclonal antibodies to induce *in vitro* cell proliferation of Th1 cells sufficient for infusion into the mammal for use in an immunotherapy treatment, wherein the *in vitro* cell proliferation is produced without the use of exogenous interleukin-2.

Babbitt *et al.* and differences from the instantly claimed methods

Babbitt discloses a method for production of "immunoreactive cells" by:

> (a) contacting a sample of mononuclear cells derived from a patient, e.g., peripheral blood mononuclear cells (PBMC), with OKT3 at or below 37° C to produce an OKT3-derived culture supernatant (T3CS);
> (b) removing the T3CS from the sample of patient- derived mononuclear cells;
> (c) determining the concentration of OKT3 in the T3CS, and if required, supplementing the T3CS with additional OKT3 to achieve a concentration of at least 0.1 ng/ml;
> (d) providing a second sample of mononuclear cells derived from the patient; and,
> (e) contacting the second sample of cells with the previously-generated T3CS for a period of time sufficient to yield a population of immunoreactive cells.

Thus, mononuclear cells are obtained and are contacted with T3CS to yield a population of immunoreactive cells. The "immunoreactive cells are described by Babbitt *et al.* as **polyclonal T-cells that exist in a primed state of activation**. Babbitt states that the cells produced by contacting with the T3CS:

> are multifunctional, i.e., possess an enhanced capacity to proliferate and produce cytokines ***upon further stimulation.*** (emphasis added)

These immunoreactive cells are stated to have a:

> low spontaneous level of immune function following processing, but are highly sensitized to respond to *low doses of second signals* up on further culture or *in vivo*.(emphasis added)

At column 4, lines 6-17, Babbitt states:

> Immunoreactive cells have a low spontaneous level of immune function following processing, but are highly sensitized to respond to low doses of second signals upon further culture, or in vivo. The immunoreactive cells of the invention **therefore require further exposure to an immune stimulant,** such as an antigen; target cell, e.g., a tumor cell or virus-infected cell; an inflammatory molecule; an adhesion molecule; an immune cell, e.g., an accessory cell; a cytokine; or any combination thereof, **to achieve full immunologic effector function.** The immunoreactive cells of the invention are multifunctional, polyclonally-activated T cells which have been generated independent of disease-specific antigens utilizing a mixture of nonspecific lymphocyte activators, i.e., autologous cytokines, and a mouse monoclonal antibody, i.e, OKT3, as synergistic stimulants.

Babbitt continues:

> The ability of EVA cells [the immunoreactive cells] to proliferate and to produce a variety of cytokines (IL-2, GM-CSF, IFN.gamma., TNF.alpha.) in vitro in response to further stimulation by such agents as PMA and IL-2, as well as to lyse tumor cell targets, is greatly enhanced compared to the PBMC from which they were derived. The lowered activation threshold of the EVA cells exhibited in vitro suggests that once they are reinfused into patients, they are likely to demonstrate enhanced responsiveness to immunological signals, such as weakly immunogenic tumor antigens which normally are non-stimulatory to unprocessed cells.

Hence the cells produced by exposure to the TC3S medium are immunoreactive cells that require further treatment. The immunoreactive cells, designated EVA cells, are cells that have low spontaneous levels of immune function following processing and require further signals to function. The Babbitt cells, as stated in Babbitt "display very little spontaneous proliferation or cytokine secretion without PMA stimulation". As stated in Babbitt (see above), the cells must have exogenous IL-2 or other stimulation to **achieve full immunologic effector function**. The cells produced by the Babbitt *et al.* require IL-2 for activation, and, hence are not Th1 cells as defined in the instant application (claims 22 and 211). Furthermore, T3CS does not contain two or more mitogenic antibodies (claim 211). It is clear that recitation of two more mitogenic antibodies does not mean two or more molecules of the same antibody (as urged by the Examiner), but means different antibodies. To render this clear, claim 211 is amended to recite that the antibodies are different.

Analysis

Anticipation requires disclosure of every element as claimed in the cited reference. Babbitt fails to disclose every element of the methods of claims 22 and/or 211 as claimed.

As discussed above, Babbitt *et al.* is directed to a method for producing immunoreactive cells by contacting a first sample of mononuclear cells with OKT3 at or below 37° C to "produce an OKT-3-derived culture supernatant (T3CS)", removing the T3CS from the mononuclear cells; optionally

supplementing the T3CS with additional OKT3 to produce a concentration of at least 0.1 ng/ml of OKT3, and then contacting a second sample of mononuclear cells with the T3CS to produce immunoreactive cells, which Babbitt states require further treatment, such as exposure to Il-2 for activation.

T3CS contains OKT3 antibodies, and may contain IL-1β, IL-6, IL-8, TNFα, TNFβ. IFN-γ, GM-CSF, IL-12, IL-10, Il-4, Il-2 and other cytokines (see, *e.g.*, col. 5, lines 47-63). Thus, patient monocytes are contacted with a composition that contains T3CS, which includes only one, not two or more, activating proteins. Further, the after contacting with the T3CS, the resulting cells are "immunoreactive cells", which as defined by Babbitt *et al.* must be activated by exposure to a second signal.

The cells produced by contacting with T3CS must be exposed to further stimulation to produce cytokines. Th1 cells are defined by their cytokine production, the cells produced by contacting with T3CS are not Th1 cells, until further stimulated. Babbitt *et al.* discloses that such further stimulation requires exposure to IL-2.

At col. 2, lines 57-61, Babbitt *et al.* states:

> By the term "immunoreactive cells" is meant polyclonal T cells that exist in a primed state of activation. Primed cells are multifunctional, i.e., they possess an enhanced capacity to proliferate *and produce cytokines upon further stimulation*. [emphasis added]

Babbitt *et al.* continues at col. 3:

> Immunoreactive cells have a low spontaneous level of immune function following processing, *but are highly sensitized to respond to low doses of second signals upon further culture, or in vivo*. The immunoreactive cells of the invention therefore require further exposure to an immune stimulant, such as an antigen; target cell, e.g., a tumor cell or virus-infected cell; an inflammatory molecule; an adhesion molecule; an immune cell, e.g., an accessory cell; a cytokine; or any combination thereof, to achieve full immunologic effector function. [emphasis added]

The cells, produced by the method, thus require exposure to a second signal, for full immunologic function.

At co l. 6, lines 19-27, Babbit *et al.* states:

> Following the incubation of cells with T3CS, the cells may be removed from the T3CS and contacted with IL-2, preferably in an amount which is sufficient to bind to at least 25% of the IL-2 receptors on the surface of the immunoreactive cells; more preferably, the amount of IL-2 is sufficient to saturate the IL-2 receptors on the surface of the immunoreactive cells.

Thus, Babbitt *et al.* teaches a method for producing immunoreactive cells that require exposure to IL-2 for full immunologic function. Therefore, the method is different from any of the instantly claimed methods, which specifically recited that the cells are caused to proliferate and expand in the absence of IL-2.

To produce that T3CS is conditioned medium Babbitt *et al.* only adds a single monoclonal antibody, OKT3. Babbitt *et al.* does not disclose or suggest the sue of with two or more proteins that interact with cell surface proteins. Hence Babbitt *et al.* is directed to a method for producing a supernatant that contains a single monclonal antibody, OKT3, to produce cells that are primed and require subsequent exposure to exogenous cytokines, particularly Il-2. Any teachings disclosure of expansion of the cells contemplates using IL-2 to effect expansion (see column 18, lines 7 -20).

The method of Babbitt *et al.* does not use mitogenic antibodies for inducing proliferation and expansion, but rather uses a supernatant and a single monoclonal antibody to produced primed cells, which then are further treated with Il-2. Furthermore, Babbitt *et al.* does not suggest the step of expanding the selected cells clinically relevant numbers in the absence of interleukin-2 (IL-2).

Thus, Babbitt discloses a method involving obtaining cells from a patient, treating the cells with a single mitogenic factor OKT3, and optionally adding exogenous cytokines (see, col. 5, lines 2-15), collecting the supernatant from such cells, and contacting the supernatant with additional cells from a patient to produce "immunoreactive cells" that require further stimulation, such as contacting with IL-2 or other exogenous cytokines. Cells produced in the first step by treatment with OKT3 and other cytokines are not the cells for re-

infusion into the patient, but are used to produce a supernatant that is used to treat cells, which then are exposed to Il-2 for expansion.

In contrast the instant methods, include the steps of differentiating leukocytes or mononuclear cells to become Th1 cells, and expanding the resulting Th1 cells to produce clinically relevant numbers of cells. Babbitt does not disclose or suggest the instantly claimed method. The description in col. 5, referenced by the Examiner refers to addition of cytokines to the T3CS supernatant, which is then used to contact cells to produce immunoreactive cells. Any description of Th1 cells, refers to production of Th1 cells in the first step of the method, which is used to produce the T3CS supernatant. Cells from the patient are then cultured in the supernatant, which contains a variety of cytokines. The resulting cells are the immunoreactive cells, referred to by Babbitt as EVA cells, **not** Th1 cells. As discussed above, the immunoreactive cells, are not Th1 cells. Therefore, Babbitt does not anticipate any of the instant claims.

Rebuttal to comments by the Examiner:

1) The Examiner states that Babbitt *et al.* "teach that said cells can be grown in the absence of IL-2 (see column 17, last paragraph)."

It is respectfully submitted that Babbit *et al.* does not teach that cells are expanded in the absence of IL-2. Contacting with T3CS (which contains only one monoclonal antibody) only results in activation of cells to produce immunoreactive cells. These immunoreactive cells then require a further signal, exposure to IL-2 to effect expansion.

> At col. 17, lines 48-65 state:
>
> Utilizing T3CS as a stimulant for mononuclear cells, it is possible to generate T cells expressing high levels of CD25/IL-2 receptors, independent of the inclusion of high levels of exogenous IL-2 in the culture medium. Although low levels of IL-2 are present in both the T3CS and EVA cultures at early timepoints, there is no detectable (< 6 pg/ml) autologous IL-2 present in the T3CS when the EVA culture is initiated. Consequently, in contrast to LAK and TIL cells which are both cultured in high levels of IL-2, the immunoreactive

> cells generated by the inventive process are presumably less dependent upon systemic administration of high dose IL-2 for therapeutic efficacy. In addition, the lack of IL-2 in the T3CS allows the production of immunoreactive cells, i.e., multifunctional, polyclonal T cells containing both $CD8^+$/cytotoxic T cells and a high percentage of $CD4^+$/helper cells, in contrast to PBMC grown in high dose IL-2 which are highly enriched in CD8+/cytotoxic T cells. Thus, the immunoreactive cells of the invention have broader functional capacities than PBMC cultured in IL-2.

Babbitt *et al.* is stating that the first signal is supplied in the absence of IL-2, not that the cells are expanded in the absence of IL-2. Babbitt *et al.* continues at col. 18, lines 7 *et seq.*:

> Following processing, the immunoreactive cells may be exposed to IL-2 at 4° C. such that IL-2 binds to at least 25% of the cell surface IL-2 receptors. Preferably, the cell surface IL-2 receptors are saturated, i.e., 100% of the IL-2 receptors on the surface of a cell are bound to IL-2, with IL-2 prior to infusion into a patient.
>
> Immunoreactive cells with cell surface bound IL-2 are likely to have an enhanced ability to expand in vivo and a decreased dependence upon helper cell-mediated IL-2 production, an activity which may be lacking or depressed in immunosuppressed cancer patients. In addition, administration of IL-2 to a patient in a cell-bound form avoids the toxicity and other clinical complications often associated with intravenous or subcutaneous co-administration of high dose IL-2 to support cell therapy.

Thus, method of Babbitt *et al.* produces immunoreactive cells that require exposure to IL-2. Therefore, the method of Babbitt *et al.* is different from those claimed in the instant application in which the cells are differentiated into Th1 cells, and then exposed, in the absence of IL-2, to signals that result in proliferation and expansion of the cells to produced cells that are not dependent upon Il-2.

2. The Examiner continues:

> The method taught by Babbitt et al. uses IFN-gamma enriched supernatants and OKT3 (*e.g.,* anti-CD3 antibody) to produce Th1 populations (see columns 5 and 6). The administered OKT3 consists of mitogenic monoclonal antibodies (*e.g.,* multiple copies of the same antibody).

As discussed above, the instant claims cannot be construed to mean that the cells are contacted with two molecules of the same antibody. The specification describes the two signals required for activation and proliferation. The claims ar amended to state that the signals are different.

The Examiner correctly states the method of Babbitt uses supernatants that contain OKT3 and that can contain IFN-γ. The supernatants, however, contain a variety of other factors, some of which direct cells to become Th1 cells, and others that direct cells to become Th2 cells. Furthermore, the cells that result at the end of the process are the "immunoreactive cells", which Babbitt *et al.* states are "multifunctional, polyclonal T cells containing both $CD8^+$/cytotoxic T cells and a high percentage of $CD4^+$/helper cells" that require exposure to additional factors, particularly IL-2, for activation. As noted above, Babbitt *et al.* states that the cells are immunoreactive cells" which are "primed cells that exist in a primed state of activation. Primed cells are multifunctional, i.e., they possess an enhanced capacity to proliferate *and produce cytokines upon further stimulation*." Babbitt *et al.* states:

> Immunoreactive cells have a low spontaneous level of immune function following processing, *but are highly sensitized to respond to low doses of second signals upon further culture, or in vivo*. The immunoreactive cells of the invention therefore require further exposure to an immune stimulant . . . .

Thus, the method is not the same as the instant method in which cells are differentiated and exposed to two signals in the absence of IL-2.

CLAIMS 22-25, 31, 32, 155-158, 164, 165, 167, 168, 211 AND 212

Claims 22-25, 31, 32, 155-158, 164, 165, 167, 168, 211 and 212 are rejected under 35 U.S.C. §102(e) as being anticipated by June *et al.* (U.S. Patent No. 6,352,694) because June *et al.* allegedly discloses that Th1 cells can be produced and expanded using treatment of CD4+ cells with anti-CD3 antibody and anti-CD28 antibody. This rejection is respectfully traversed.

The claims

Each of the independent claims includes a step in which Th1 cell differentiation is effected by treating the cells with either or both interferon-γ and IL-2, or anti-Il-4 antibody or αB7.2 mAb or TGF-β. Claim 22 and 211 are discussed above.

Claim 155 is directed to a method for generating clinically relevant numbers of Th1 cells by:

(a) collecting material comprising body fluid or tissue containing mononuclear cells from a mammal;
(b) treating the cells to induce differentiation of mononuclear cells into Th1 cells; and
(c) contacting the resulting differentiated cells with two or more activating proteins specific for cell surface proteins present on the cells in an amount sufficient to induce *ex vivo* cell expansion, whereby clinically relevant numbers of cells for autologous cell therapy are generated, wherein the contacting is effected in the absence of exogenous IL-2.

Analysis

June *et al.* does not disclose a differentiation of Th1 cells by treatment with either or both interferon-γ and IL-2, or anti-Il-4 antibody or αB7.2 mAb or TGF-β. Since anticipation requires disclosure of every element as claimed, June *et al.* does not anticipate any of the claims.

THE REJECTION OF CLAIMS 22-25, 28, 29, 31-33, 155-158, 164-168, 170-172, 211-213, 216 and 217 UNDER 35 U.S.C. § 103(a)

Claims 22-25, 28, 33, 211-213 and 217

Claims 22-25, 28, 33, 211-213 and 217 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Babbitt *et al.* (U.S. Patent No. 5,766,920) in view of Cracauer because Babbitt allegedly teaches methods of producing Th1 cells and Cracauer teaches the use of a hollow fiber bioreactor for expanding cells. This rejection is respectfully traversed.

Relevant law

In order to set forth a prima facie case of obviousness under 35 U.S.C. §103, the differences between the teachings in the cited reference

must be evaluated in terms of the whole invention, the prior art must provide a teaching or suggestion to the person of ordinary skill in the art to have made the changes that would produce the claimed product. See, e.g., Lindemnann Maschinen-fabrik Gmbh v. American Hoist and Derrick Co., 730 F.2d 1452, 1462, 221 USPQ 481, 488 (Fed. Cir. 1984). The mere fact that prior art may be modified to produce the claimed product does not make the modification obvious unless the prior art suggests the desirability of the modification. In re Fritch 23 USPQ 1780 (CAFC 1992); see, also, In re Papesh, 315 F.2d 381, 137 USPQ 43 (CCPA 1963).

The Claims

The claims are discussed above.

Analysis

As discussed above, Babbitt *et al.* does not teach or suggest the instantly claimed method. Babbitt *et al.* is deficient in failing to teach a method in which cells are contacted with two signals in the absence of Il-2. Babbitt *et al.* teaches a method in which a supernatant that contains OKT3 is produced. The supernatant is used to treat additional cells from a patient to produce EVA (*ex vivo* activated) cells that are immunoreactive cells, which as discussed above are **polyclonal T-cells that exist in a primed state of activation** that are:

> are multifunctional, i.e., possess an enhanced capacity to proliferate and produce cytokines ***upon further stimulation.*** (emphasis added)

These immunoreactive cells are stated by Babbitt to have a:

> low spontaneous level of immune function following processing, but are highly sensitized to respond to *low doses of second signals* up on further culture or *in vivo*.(emphasis added)

The cells require Il-2.

Cracauer, which teaches a bioreactor, does not cure the deficiencies in the teachings of Babbitt. Therefore, the Examiner has failed to set forth a *prima facie* case of obviousness.

Claims 22-25, 31-33, 155-158, 164-168, 170-172, 211-213, 216 and 217

Claims 22-25, 31-33, 155-158, 164-168, 170-172, 211-213, 216 and 217 are rejected under 35 U.S.C. § 103(a) as being unpatentable over June *et al.* (U.S. Patent No. 6,352,695) in view of Cracauer because June *et al.* allegedly teaches methods of producing Th1 cells "without the use of exogenous lymphokines" and Cracauer teaches the use of a hollow fiber bioreactor for expanding cells. This rejection is respectfully traversed.

As discussed above, June *et al.* fails to teach or suggest a method in which cells are differentiated into Th1 cells by activating them in the presence of either or both interferon-γ and IL-2 or anti-Il-4 antibody or αB7.2 mAb or TGF-β, whereby cells differentiate into Th1 cells. Cracauer *et al.* fails to teach or suggest this step. Therefore the combination of June *et al.* and Cracauer *et al.* does not result in the instantly claimed methods.

Claims 22-25, 28, 29, 31, 211 and 216

Claims 22-25, 28, 29, 31, 211 and 216 are rejected under 35 U.S.C. §103(a) as being unpatentable over Babbitt in view of O'Garra *et al.* because O'Garra allegedly teaches that IL-4 antibody treatment of CD4+ cells favors development of Th1 cells so that it would have been obvious to one of ordinary skill in the art to have produced Th1 cells. This rejection is respectfully traversed.

Babbitt

The teachings of Babbitt are discussed above. As discussed above, Babbitt *et al.* teaches a method for producing **polyclonal T-cells that exist in a primed state of activation** as discussed above, by exposing mononuclear cells to medium that contains a single monoclonal antibody. The cells then require exposure to IL-2. Therefore, Babbitt *et al.* does not disclose a method in which cells are produced in the absence of IL-2, nor a method in which cells are exposed to two or more signals, such as mitogenic monoclonal antibodies specific for different cell surface proteins.

O'Garra *et al.*

O'Garra *et al.* is directed to a study to assess the role of cytokines in determining T-lymphocyte function. O'Garra *et al.* teaches that encounter with a host antigen can result in either cell-mediated or humoral classes of immune response and that these responses are attributable to the heterogeneity of $CD4^+$ T cells. O'Garra *et al.* further teaches that mouse $CD4^+$ T cell clones can be divided into two predominant cytokine secretion profiles designated Th1 , which produce IL-2 and IFN-γ and other factors that promote delayed-type hypersensitivity reactions, and Th2, which produce Il-4, Il-5 and IL-10. The subsets by virtue of the differing cytokine profiles cross-regulate immune responses. O'Garra *et al.* states (page 459, col. 1) that the ability to control the emerging Th cell phenotype [*in vivo*] following exposure to antigen offers the potential to induce a response appropriate for each pathogen. O'Garra presents the results of studies designed to elucidate the pathways by which each type of subset is induced. O'Garra *et al.* concludes (page 462):

> . . . The question of whether Th1 and Th2 cells all arise from a common precursor, possibly a Th0-type cell, and whether such populations are malleable or can be differentiated further, remains *an unresolved issue*, with important implications for the treatment of chronic disease. (emphasis added)

Thus O'Garra *et al.* does not teach that populations of Th1 and Th2 cells can be produced and does not teach how to produce such populations.

Therefore, O'Garra *et al.* concludes that it is not clear whether Th1 and Th2 phenotypes can be altered; it does not teach or suggest production of compositions of either predominantly Th1 or Th2 cells, and certainly does not provides any motivation to produce large number or high densities of cells of any type.

O'Garra *et al.* does not cure the deficiencies in the teachings of Babbitt. Therefore, the combination of teachings of Babbitt and O'Garra *et al.* does not result in the instantly claimed methods. Therefore, the Examiner has failed to set forth a *prima facie* case of obviousness.

Claim 32

Claim 32 is are rejected under 35 U.S.C. § 103(a) as being unpatentable over Babbitt *et al.* (U.S. Patent No. 5,766,920) in view of Cracauer as applied to claims 22-25 28, 29, 31, 211 and 216 above 2 and further in view of June *et al.* (International PCT application No. WO 94/29436 or U.S. Patent No. 5,858,358) because June *et al.* teaches expansion of cells using anti CD3 and anti CD28 antibodies. This rejection is respectfully traversed.

As discussed above, the combination of Babbitt and O'Garra *et al.* does not result in any of the claimed methods because the combination does not suggest a method for producing clinically relevant numbers of Th1 cells by differentiating cells by activating in the presence of cytokines or other agent that produce Th1 cells and expanding and proliferating in the presence of two signals.

June *et al.*

June *et al.* teaches a method for inducing a population of T cells to proliferate by providing a first signal to activate the cells and then a second signal to stimulate proliferation. Activation of T cells is accomplished by contacting the cells with anti-CD3 antibody or anti-CD2 antibody. Proliferation is induced by contacting an activated population of T-cells with a second agent, such as anti-CD28 antibody, that stimulates an accessory molecule on the T cell surface. June *et al.* does not teach the step of first causing differentiation of the cells into Th1 cells and then expanding and proliferating in the presence of two signals, such as anti-CD3 antibody or anti-CD2 antibody and anti-CD28 antibody.

Therefore, the combination of teachings of the cited references does not result in the instantly claimed methods. The Examiner has failed to set forth a *prima facie* case of obviousness.

Claims 22-25, 31, 32, 155-158, 162, 164, 165, 167, 168, 211, 212

Claims 22-25, 31, 32, 155-158, 162, 164, 165, 167, 168, 211, 212 are rejected under 35 U.S.C. § 103(a) as being unpatentable over *et al.* (U.S. Patent No. 6,352,694) in view of Sedar *et al.* because June *et al.* teaches that Thl cells can be produced and expanded using by treatment of CD4+ cells with anti-CD3 antibody and anti-CD28 antibody with out not use exogenous lymphokines, but that June *et al.* fails to teach treatment with interferon gamma. Seder *et al.* is alleged to teach that Th1 cells can be produced by treating CD4+ cells with interferon gamma so that it allegedly

> would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have created the claimed invention because June *et al.* teach the claimed method except for the use of interferon gamma treatment, while Seder *et al.* teaches that Th1 (*e.g.*, interferon-gamma producing cells derived from CD4+ T cells) can be produced by treating CD4+ cells with interferon gamma (see page 10190, second column, last paragraph, first sentence).

This rejection is respectfully traversed.

The cited references

June *et al.* is discussed above.

Seder *et al.* merely teaches that activation of cells in the presence of IL-12 or interferon-γ leads to the formation of Th1-like cells.

Analysis

As discussed above, the methods taught by June *et al.* differs from the instantly claimed methods because they do not include steps of differentiating cells to produce Th1 cells and then inducing cell proliferation and expanding the cells. In the method of June *et al.*, $CD4^+$ cells are contacted with anti-CD3 and anti-CD28. June *et al.* does not indicate any reason, nor does there appear to be any such reason, to differentiate the cells into Th1 cells prior to inducing cell proliferation and expansion. According to June *et al.*, its method produces Th1-enriched cell populations. Sedar *et al.* merely teaches that activation of cells in

the presence of produces Th1 cells, but does not provide any motivation to modify the method of June *et al.*

The mere fact that prior art may be modified to produce the claimed product does not make the modification obvious unless the prior art suggests the desirability of the modification. In re Fritch 23 USPQ 1780 (CAFC 1992); see, also, In re Papesh, 315 F.2d 381, 137 USPQ 43 (CCPA 1963). Since neither reference suggests the desirability of a modification of the method of June *et al.*, such modification is not obvious.

* * *

In view of the above remarks and the amendments and remarks of record, consideration and allowance of the application are respectfully requested.

Respectfully submitted,
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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: MICHEAL L. GRUENBERG

Serial No.: 08/700,565

Filed: July 25, 1996

For: AUTOLOGOUS IMMUNE CELL THERAPY: CELL COMPOSITIONS, METHODS AND APPLICATIONS TO TREATMENT OF HUMAN DISEASE

Art Unit: 1644

Examiner: Schwadron, R

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Debra Walker

MARKED UP CLAIMS (37 C.F.R. § 1.121)

Please amend claims 22, 29, 155, 157, 170 and 211 as follows:

22. (Amended) A method for generating clinically relevant cell numbers of Th1 cells, comprising:

(a) collecting material containing mononuclear T lymphoid cells from a mammal;

(b) activating the T lymphoid cells to alter their cytokine production profile by causing differentiation of the cells into Th1 cell, wherein the cells are activated in the presence of either or both interferon-γ and IL-2 or anti-Il-4 antibody or αB7.2 mAb or TGF-β, whereby cells differentiate into Th1 cells; and

(c) in the absence of exogenous Il-2, inducing cell proliferation and expanding the cells under conditions that produce at least about 10^{10} cells/liter of a homogeneous population of Th1 cells, wherein:

a homogeneous population of Th1 cells comprises greater than about 50% Th1 cells; and

the resulting cells do not require co-infusion of Il-2 for activity.

29. (Amended) The method of claim [28] 22, wherein anti-IL-4 monoclonal antibodies are also present during activation.

155. (Amended) A method for generating clinically relevant numbers of Th1 cells for autologous cell therapy, comprising:

(a) collecting material comprising body fluid or tissue containing mononuclear cells from a mammal;

(b) treating the cells to induce differentiation of mononuclear cells into Th1 cells, wherein the cells are treated with either or both interferon-γ and IL-2, or anti-Il-4 antibody or αB7.2 mAb or TGF-β to induce differentiation of Th1 cells; and

(c) contacting the resulting differentiated cells with two or more different activating proteins specific for cell surface proteins present on the cells in an amount sufficient to induce *ex vivo* cell expansion, whereby clinically relevant numbers of cells for autologous cell therapy are generated, wherein the contacting is effected in the absence of exogenous [cytokines] IL-2.

157. (Amended) The method of claim 155, wherein the treating[and contacting steps] step occurs in the absence of exogenous cytokines.

170. (Amended) The method of claim 155, wherein the expanded cells are predominantly Th1[, Th2, Th3] cells.

211. (Amended) A method for generating immune cells for autologous cellular immunotherapy, comprising:

collecting leukocyte containing material from a mammal;

differentiating the leukocytes into Th1 cells by contacting the cells with a composition comprising interferon-γ, or anti-Il-4 antibody or αB7.2 mAb or TGF-β; and

exposing the leukocyte containing material to two or more mitogenic different monoclonal antibodies to induce *in vitro* cell proliferation of Th1 cells sufficient for infusion into the mammal for use in an immunotherapy treatment, wherein the *in vitro* cell proliferation is produced without the use of exogenous interleukin-2.